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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,317	05/31/2005	Sunil Shaunak	POLYT 9351 WO-US	3774

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,317	SHAUNAK ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/3/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 48-139* is/are pending in the application.

4a) Of the above claim(s) *50,56-58,62,70,74-77,81,88-91,99 and 103-139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,48,49,51-55,59-61,63-69,71-73,78-80,82-87,92-98 and 100-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/15/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/22/2005 and 3/3/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1 and 48-139 are currently pending.

Election/Restrictions

Applicants' election of group I (claims 1, 48-73, 78-87, and 92-102) and the election of the following species: dendrimer generation 3.5-glucosamine, glucosamine 6-phosphate, and severe sepsis, in the reply filed on 3/3/2009 are acknowledged. During a telephone conversation with the applicant's attorney, Matthew Kaser on April 30, 2009, a provisional election was further clarified with traverse to prosecute the species of a carboxylic terminated PANAM dendrimer generation 3.5 covalently linked to glucosamine 6-phospahte with no further modification. Affirmation of this election must be made by applicant in replying to this Office action.

Applicants stated that the box for "unity of invention is unchecked in the international search report (ISR) mailed on 7/29/2003, thus the examiner is in error. An opinion in the ISR is nonbinding in the examination of national stage application. See 1845.01: "On the international level, all written opinions are nonbinding and a patent does not issue; what does issue is an international preliminary report on patentability (IPRP), which is nonbinding on the elected States". Also, Applicants stated that the examiner erred in not stating which categories the claims of Groups I-IV encompass. However, the examiner clearly categorized as product, method of

using *in vivo*, method of making, and method of using *in vitro*, respectively in the previous action mailed on 2/4/2009. See 37 CFR 1.475:

> Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage.
>
> (a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention "). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features " shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
>
> (b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
>
> (1) A product and a process specially adapted for the manufacture of said product; or
>
> (2) A product and a process of use of said product; or
>
> (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
>
> (4) A process and an apparatus or means specifically designed for carrying out the said process; or
>
> (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.
>
> (c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.
>
> (d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).
>
> (e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

As set forth in Rule 13.1 of the Patent Cooperation Treaty (PCT), "the international application shall relate to one invention only or to a group of inventions." Moreover, as stated in Rule 13.2 PCT, Unity of Invention is satisfied "where a group of inventions is claimed in one and the same international application, the requirement of unity referred to in Rule 13.1 shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole makes over the prior art so linked as to form a single general

inventive concept. The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking the claims is a glycodendrimer. Prior art exists which causes the glycodendrimer in the instant application to lack a special technical feature. Glycodendrimer has been previously disclosed in Rockendorf *et al.* (Topics in Current Chemistry, 217: 2001, Fig 7). Therefore, the feature linking the claims does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

Accordingly, Groups I-IV are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept. Therefore, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. In addition, search burden being undue is a moot argument for lack of unity issue. Undue search burden is not an issue in a lack of unity. With regard to the species election, the same response stated above is applied to the same arguments. In addition, search burden being undue is a moot argument for lack of unity issue. Undue search burden is not an issue in a lack of unity.

Claims 50, 56-58, 62, 70, 74-77, 81, 88-91, 99, and 103-139 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group or species, there being no allowable generic or linking claim. Claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 are under examination in the instant office action.

Priority

The instant application is a 371 of PCT/GB03/01133 filed on 3/18/2003 and claims benefit of foreign application filed on 4/19/2002. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). A certified copy of foreign application has been submitted on 10/15/2004.

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 3/18/2003.

Information Disclosure Statement

Signed and initialed copies of the information disclosure statement filed on 7/22/2005 and 3/3/2009 are enclosed in this action.

Claim objections

Claims 54, 59-60, and 78 are objected because of the following informalities: typographical errors. The terms "sulphated" in claim 54 and "sulphate" in claims 59-60 and 78 should be corrected to --sulfated-- and --sulfate--.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 48-49, 51-55, 59-61, 63-69, 71-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims recite a generic genus, *i.e.*, generic glycodendrimer comprising carbohydrate moieties covalently linked to a carboxylic terminated dendrimer.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43

USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Applicants provide no description of the claimed generic glycodendrimer, either in word, by structure, by formula, by chemical name, or by physical properties that would indicate that Applicants were in possession of the claimed generic glycodendrimer at the time of the invention. The only disclosed examples of dendrimer and carbohydrate moiety is a carboxylic terminated poly(amidoamine) dendrimer (PAMAM dendrimer) generation 3.5 and glucosamine or modified glucosamine such as glucosamine 6-sulphate in the specification, they are not representatives of species falling within the scope of the claimed genus since the term "glycodendrimer" was interpreted as a designation for carbohydrate-containing molecules which can be grown generationwise following an iterative repetitive synthesis and there are various types of dendrimers other than PAMAM dendrimer (see Rockendorf *et al.* cited above). In addition, carbohydrate moiety encompasses disaccharide, trisaccharide, oligosaccharide, and polysaccharide as well as monosaccharide such as glucosamine. However, there is no example concerning disaccharide, trisaccharide, oligosaccharide, and polysaccharide as carbohydrate

moiety other than glucosamine or modified glucosamine. Furthermore there is no information about how many molecules of carbohydrate are attached to a dendrimer. In addition, Applicants do not describe the structural features of such glycodendrimer that would possess the claimed activity.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78, 80, 82-87, 92-98, and 100-102 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PAMAM generation 3.5-glucosamine or glucosamine modified with sulfate or acetyl group, does not reasonably provide enablement for the other glycodendrimers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to

consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (Balls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All factors have been considered together and specifically relevant factors are addressed below:

The nature of the invention and the breadth of the claims: The claims are drawn to a generic glycodendrimer comprising carbohydrates moieties linked to a carboxylic terminated dendrimer. The "glycodendrimer" encompasses carbohydrate-containing molecules which can be grown generationwise following an iterative repetitive synthesis and there are various types of dendrimers depending on repetitive base molecule. In addition, carbohydrate moiety attached to the dendrimers encompasses disaccharide, trisaccharide, oligosaccharide, and polysaccharide as well as monosaccharide. Thus, the number of theoretically conceivable glycodendrimers as claimed is in millions rendering the scope of the claims large.

The state of the prior art: Generally, the relative skill of those in the art of pharmaceuticals and pharmacology is high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant composition for accomplishing the desired result of the claimed invention without undue experimentation. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies

inversely with the degree of unpredictability of the factors involved". See In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

The predictability or unpredictability of the art: Malik *et al.* (J controlled Release 65:133-148, 2000) teaches that dendrimers are highly branched macromolecules of low polydispersity that provide many exciting opportunities for design of novel drug-carriers, gene delivery systems and imaging agents and hold promise in tissue targeting applications, controlled drug release (abstract). They disclosed several dendrimer including amine terminated dendrimers (cationic dendrimer) and carboxylic acid terminated dendrimer (anionic dendrimer), which were used to study systematically the effect of dendrimer generation and surface functionality on biological properties in vitro (abstract, table 1, and figure 1). They show that dendrimers have huge difference in molecular weight and the number of surface groups depending on the generation, that is, the higher generation has the higher molecular weight and the more surface groups (Table I). In addition, their study shows that cytotoxic or haemolytic effects and bio-distribution of dendrimers vary depending on type of repetitive base molecules and generations. For example, anionic PAMAM dendrimers (gen 2.5, 3.5 and 5.5) showed longer circulation times (~20–40% recovered dose in blood at 1 h) with generation-dependent clearance rates; lower generations circulated longer. While polyether dendrimers bearing carboxylate are haemolytic, the anionic PAMAM and DAB dendrimers were not haemolytic up to concentration of 2 mg/ml, but the higher generation carboxylate PAMAMs were (Fig 4 and p142, col 2, para2). These data provide evidence that depending on the generation and types of repetitive base molecule, different types of dendrimers have different biocompatibility, thus one of ordinary skill in the art would not expect that any generation of dendrimer or any type of dendrimers based on different

repetitive base molecule would have similar biological activities as claimed. Furthermore, there is no prior art teaching dendrimer linked with oligosaccharides and polysaccharides. It is unpredictable what specific embodiment of the million possibilities of the instant claims would have the desired biological properties. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The amount of direction or guidance presented and the presence or absence of working examples: The only disclosed working example of dendrimer and carbohydrate moiety is a carboxylic terminated poly(amidoamine) dendrimer (PAMAM dendrimer) generation 3.5 and glucosamine or modified glucosamine such as glucosamine 6-sulphate in the specification (fig. 1b). However, they are not representatives of species falling within the scope of the claimed genus as stated above. In addition, carbohydrate moiety encompasses disaccharide, trisaccharide, oligosaccharide, and polysaccharide as well as monosaccharide such as glucosamine. However, there is no example concerning disaccharide, trisaccharide, oligosaccharide, and polysaccharide as carbohydrate moiety other than glucosamine or modified glucosamine. Furthermore there is no information about how many molecules of carbohydrate are attached to a dendrimer. In addition, Applicants do not describe the structural features of such glycodendrimer that would possess the claimed activity. Applicants disclosed *in vitro* assays showing the effects of dendrimer generation 3.5 –glucosamine 6-sulfate (31-60), however, there is no disclosure regarding other types of glycodendrimers with regard to "how to make" and "how to use" aspects.

The Quantity of Experimentation Needed. Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a glycodendrimer out of the plethora of possibilities encompassed by the instant claims that would have desired biological properties.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rockendorf *et al.* (Topics in Current Chemistry, 217: 2001) in view of Malik *et al.* (J controlled Release 65:133-148, 2000, supplied by Applicants) and US 2003/0114418 (pub date: 6/19/2003, effective filing date: 8/14/2001).

Rockendorf *et al.* teaches glycodendrimers, which have become valuable tools in glycobiology especially in the context of multivalency which is an important principle of carbohydrate-protein interactions (abstract). It further teaches that sugarcoated noon-carbohydrate dendrimers, which serves as a scaffold for the multiple presentation of sugar moieties, which are known as the principal carbohydrate epitopes in particular glycobiological systems (p205, para 1). Also, it teaches that the phenomenon of multivalency adds to the

strength of carbohydrate-protein interaction that is needed for a significant biological effects and thus the week affinity of singular interacting is multiplied to an overall avidity with binding constants in the nanomolar range (p205, para 2). The multivalent glycodendrimers are developed as glycomimetics to interfere carbohydrate-protein interaction, wherein protein-carbohydrate complexation is important in a wide range of medically significant interactions including signal transduction, inflammation, and microbilogical pathogenesis (p207, para 2). It discloses various types of glycodendrimer such as a cationic polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery (p203, para 3 and figure 1 and 7) and N-acetyl-glucosamine-functionalized dendrimers (scheme 2 and p209, para 1).

The reference differs from the instant claims insofar as it does not specifically teach glucosamine 6-sulfate linked to PAMAM dendrimer generation 3.5 and the concentration of glycodendrimer. In addition, it is silent about treating severe sepsis recited in claims 61, 63-65, 69, 71-73, 80, and 82-84 and decreasing chemokine or cytokine level and decreasing angiogenesis recited in claims 92-97.

Malik *et al.* teaches that dendrimers are highly branched macromolecules of low polydispersity that provide many exciting opportunities for design of novel drug-carriers, gene delivery systems and imaging agents and hold promise in tissue targeting applications, controlled drug release (abstract). They disclosed several dendrimer including amine terminated PAMAM dendrimers (generation 1-4) and carboxylic acid terminated PAMAM dendrimer (generation 1.5, 2.5, 3.5, 5.5, 7.5, and 9.5), which were used to study systematically the effect of dendrimer generation and surface functionality on biological properties *in vitro* (abstract, table 1, and figure

1). The study shows that cationic dendrimers such as PAMAM dendrimers bearing -NH_2 termini were generally haemolytic and cytotoxic dependent on molecular weight (generation) and the number of surface groups displaying IC_{50} values 50–300 μg/ml dependent on dendrimer-type, cell-type and generation (abstract) while anionic dendrimers such as PAMAM dendrimer bearing carboxylic termini were neither haemolytic nor cytotoxic over a broad concentration range up to concentration of 2 mg/ml (2000 μg/ml) (abstract, p142, col 2, para 2, and table 3). It further teaches that for a polymeric carrier to be suitable for *in vivo* application it is essential that the carrier is nontoxic and nonimmunogenic, and it should preferably be biodegradable (p134, col 2, para 2). In addition, it disclosed an specific use of PAMAM generation 3.5 as a drug carrier for tumor targeting such as PAMAM generation 3.5–palatinate, which is able to selectively increase the platinum content of palpable B16F10 subcutaneous tumors approximately 50-fold compared to that seen after i.v. administration of cisplatin at its maximum tolerated dose (p146, col. 2, para 2).

US 2003/0114418 teaches a method of treating inflammation or inflammation-associated disorder by administrating glucosamine in combination with cyclooxygenase 2-selective inhibitor, wherein the glucosamine is selected from the group consisting of glucosamine, glucosamine salts of hydrochloric, iodic, sulfuric, phosphoric, or other pharmaceutically acceptable acid; glucosamine-2-sulfate; glucosamine -3-sulfate; glucosamine -6-sulfate; glucosamine -2,3-disulfate; glucosamine- 2,6-disulfate; glucosamine -3,6-disulfate; glucosamine-3,4,6-trisulfate; glucosamine pentaacetate; glucosamine-1-phosphate; glucosamine-6-phosphate; N-acetylglucosamine-6-phosphate; N-acetylglucosamine-1-phosphate; N-acetyl-D-glucosamine; uridine diphosphate (UDP)-N-acetylglucosamine; and mixtures thereof (claims 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use carboxylic termiated PAMAM dendrimer generation 3.5 taught by Malik *et al.* as a drug delivery carrier of glucosamine derivatives such as glucosamine 6-sulfate in order to make a non-cytotoxic and biocompatible glycodendrimer because of the following reasons: Dendrimers have been taught to be useful carriers for therapeutic agents by prior art. Rockendorf *et al.* already discloses a polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery and N-acetyl-glucosamine-functionalized dendrimers. Malik *et al.* teaches that cationic dendrimers were generally haemolytic and cytotoxic dependent on molecular weight (generation) and the number of surface groups while anionic dendrimers such as PAMAM dendrimer bearing carboxylic termini were neither lytic nor cytotoxic over a broad concentration range. Thus, the skilled artisan would have been motivated to modify the glycodendrimers taught by Rockendorf *et al.* by using PAMAM dendrimer bearing carboxylic termini, which are less cytotoxic and haemolytic compared to cationic PAMAM dendrimer. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute any glucosamine derivative such as glucosamine 6-sulfate for N-acetyl-glucosamine since they are known to be functional equivalent as taught by US 2003/0114418.

With regard to the concentration of glycodendrimer, one of ordinary skill in the art at the time of invention would have been motivated to optimize the concentration of glycodendrimer based on IC_{50} values of PAMAM dendrimers taught by Malik *et al.* in order to avoid cytotoxic and haemolytic effects. The effective dosage of the composition of the present invention can be determined according to age, gender, severity of condition, absorption of an active ingredient,

dosage forms, types of vehicles used with the active ingredients, inactivation rate, excretion and other medicines applied together. In addition, it is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ 33; *In re Russell*, 169 USPQ 426. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

With regard to treating severe sepsis recited in claims 61, 63-65, 69, 71-73, 80, and 82-84 and decreasing chemokine or cytokine level or decreasing angiogenesis recited in claims 92-97, the instant invention is directed to a product or a composition, thus an intended use, which are treating severe sepsis, decreasing chemokine or cytokine level or decreasing, does not have a patentable weight. In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be new. If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statutes make no provision for patenting of an article or composition which is not, in and of itself, new.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-071818. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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